Editorial Commentary

New first-line treatment for recurrent or metastatic squamous cell carcinoma of head and neck: does one size fit all?

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Background

According to cancer statistics for 2012 (GLOBOCAN), the global incidence of HNC in that year stood at around 680,000, with 390,000 of these cases occurring in Asian countries. Around 240,000 Asian people died from HNC, accounting for 5.5% of global cancer deaths (1). Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) have a poor prognosis. Treatment goals are limited, but include prolongation of survival, palliation of existing symptoms and prevention of new cancer-related symptoms. In particular, systemic chemotherapy has only a modest impact on outcome in these patients (2), and median survival in reported Phase III randomized trials ranges from 6 to 9 months (3-8). Platinum-based chemotherapy remains the standard, and although combination therapy has shown higher response rates, no other regimen has demonstrated a survival advantage over cisplatin monotherapy. In their randomized Phase III trial of cisplatin or carboplatin plus 5-FU (PF/CF) with or without cetuximab against PF/CF for R/M SCCHN (EXTREME Study), Vermorken *et al.* reported that the hazard ratio for overall survival (OS) of PF/CF plus cetuximab to PF/CF alone was 0.80 [95% confidence interval (CI), 0.64–0.99]. Median OS was 10.1 months for PF/CF plus cetuximab versus 7.4 months for PF/CF alone (P=0.04) (9). From this result, PF/CF + cetuximab, the so-called EXTREME regimen, has been the standard first line chemotherapy for patients with R/M SCCHN. For platinum-refractory R/M SCCHN, the anti-PD-1 antibodies nivolumab and pembrolizumab demonstrated a survival benefit in the pivotal Phase III trials (CheckMate141, KEYNOTE-040) (10,11). Recently, however, Burtness *et al.* reported the practice-changing results of a Phase III trial (KEYNOTE-048; KN-048) which compared the EXTREME regimen with pembrolizumab alone or PF/CF plus pembrolizumab for patients with previously untreated R/M SCCHN (12).

KEYNOTE-048

KN-048 was a randomized phase III trial of patients with previously untreated R/M SCCHN. Patients were stratified by PD-L1 expression (TPS: tumor proportion score), p16 status and performance status and randomized in a 1:1:1 ratio to pembrolizumab alone, PF/CF plus pembrolizumab and the EXTREME regimen as the standard arm. The primary endpoints were OS and progression-free survival (PFS) in the intention-to-treat (ITT) population (12). The statistical methods were markedly complex, and likely left many oncologists uncertain of their validity, and wondering whether they represent a suitable direction for oncology to pursue. There were 14 primary hypotheses: the superiority of pembrolizumab alone and of PF/CF plus pembrolizumab versus the EXTREME regimen for OS and PFS with a PD-L1 CPS (combined positive score) of 20 or more, CPS of 1 or more, and the total population; and the non-inferiority (non-inferiority margin: 1.2) of pembrolizumab alone and of PF/CF plus pembrolizumab

versus the EXTREME regimen for overall survival in the total population. Of these 14 primary hypotheses, six were tested first, in parallel: superiority of pembrolizumab alone and of PF/CF plus pembrolizumab versus the EXTREME regimen for OS and PFS in PD-L1 CPS ≥20, superiority of PF/CF plus pembrolizumab versus EXTREME regimen for PFS and non-inferiority of PF/CF plus pembrolizumab versus EXTREME regimen for OS. The remaining eight hypotheses were then tested hierarchically to control for an overall one-sided type I error of 0.025 based on the orders of CPS ≥20, ≥1 and ITT. The pre-defined treatment outcomes are summarized in *Table 1*. From the results, pembrolizumab alone was superior to the EXTREME regimen in the population of CPS ≥20 and ≥1 and non-inferior to the EXTREME regimen in the ITT population, while PF/CF plus pembrolizumab was superior to the EXTREME regimen in the populations of CPS ≥20, ≥1 and ITT. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) consequently approved pembrolizumab alone for previously untreated R/M SCCHN in patients expressing PD-L1 (CPS) ≥1, and approved PF/CF plus pembrolizumab for previously untreated R/M SCCHN, albeit that EMA restricted this approval to patients expressing PD-L1 (CPS) ≥1.

However, a detailed analysis of KN-048 raises questions about whether pembrolizumab alone or PF/CF plus pembrolizumab can take all places of the EXTREME regimen. This is because the KN-048 paper provides no information about the efficacy of pembrolizumab alone or PF/CF plus pembrolizumab in the 1≤ CPS <20 and CPS <1 population. From the summarized results of *Table 1*, we assume that the robust effectiveness in the CPS ≥20 population, which generally accounts for around 40% of these patients, cast a positive result over the total population. If so, applying the results of KN-048 into clinical practice should be done with care, because the benefit of pembrolizumab alone or PF/CF plus pembrolizumab against the EXTREME regimen may be less than expected for the CPS 1–19 and CPS<1 population. These questions are further addressed in the EMA (European Medicines Agency) assessment report (Procedure No. EMEA/H/C/003820/II/0065, https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0065-epar-assessment-report-variation_en.pdf), which describes the post-hoc exploratory analysis of KN-048 focusing on the CPS 1–19 and CPS <1 population, summarized in *Table 2*. For the CPS 1–19 population, median OS of pembrolizumab alone and the EXTREME regimen were closely similar, while the overall response rate (ORR) of pembrolizumab alone was lower than that of EXTREME regimen. On the other hand, median OS of PF/CF plus pembrolizumab was better than that of the EXTREME regimen and ORR of PF/CF plus pembrolizumab was closely similar to it. In the CPS <1 population, median OS of pembrolizumab alone appeared to be worse than that of the EXTREME regimen and ORR was much lower. In contrast, the median OS of PF/CF plus pembrolizumab was closely similar to that of the EXTREME regimen while ORR appeared to be lower. These findings show that pembrolizumab alone most benefits the CPS ≥20 population while PF/CF plus pembrolizumab most benefits the CPS ≥1 population.

With regard to adverse events, pembrolizumab alone had a better safety profile than the PF/CF plus pembrolizumab or EXTREME regimens, with rates of any grade 3 or worse adverse events of 55% with pembrolizumab alone, 85% with PF/CF plus pembrolizumab and 83% with the EXTREME regimen. In terms of adverse events of interest (so-called immune-related adverse events), events of any grade occurred in 31% with pembrolizumab alone and 26% with PF/CF plus pembrolizumab. There were no new safety concerns for pembrolizumab or PF/CF plus pembrolizumab.

Combining the above efficacy and safety information for each treatment option, and considering patient condition and disease status, we propose a new treatment algorithm for patients with previously untreated SCCHN.

For patients with previously untreated platinum-sensitive R/M SCCHN:

(I) Asymptomatic and stable patients:
  (i) CPS ≥20: pembrolizumab alone;
  (ii) 1≤ CPS <20: PF/CF plus pembrolizumab or pembrolizumab alone;
  (iii) CPS <1: PF/CF plus pembrolizumab or EXTREME regimen;

(II) Symptomatic or progressive patients:
  (i) CPS ≥20: PF/CF plus pembrolizumab or pembrolizumab;
  (ii) 1≤ CPS <20: PF/CF plus pembrolizumab;
  (iii) CPS <1: EXTREME regimen or PF/CF plus pembrolizumab.

Conclusions

Burtness *et al.* demonstrated better treatment outcomes with pembrolizumab alone and PF/CF plus pembrolizumab than

Table 1 Summary of the pre-defined outcomes of KEYNOTE-048 from primary manuscript (12)

Treatment arms	Pembrolizumab *vs.* EXTREME						Pembrolizumab plus chemotherapy *vs.* EXTREME					
PD-L1	CPS ≥20		CPS ≥1		ITT		CPS ≥20		CPS ≥1		ITT	
Treatment	P (N=133)	E (N=122)	P (N=257)	E (N=255)	P (N=301)	E (N=300)	PC (N=126)	E (N=110)	PC (N=242)	E (N=235)	PC (N=281)	E (N=278)
OS (median), M	14.9	10.7	12.3	10.3	11.6	10.7	14.7	11.0	13.6	10.4	13.0	10.7
HR (95% CI)	0.61 (0.44–0.78)		0.78 (0.64–0.96)		0.83 (0.70–0.99)		0.60 (0.45–0.82)		0.65 (0.53–0.80)		0.72 (0.60–0.87)	
P value	0.0007*		0.0086*		0.0199†		0.00044*		0.00002*		0.00025*	
PFS (median), M	3.4	5.0	3.2	5.0	2.3	5.2	5.8	5.2	5.0	5.0	4.9	5.1
HR (95% CI)	0.99 (0.75–1.29)		1.16 (0.96–1.39)		1.34 (1.13–1.59)		0.73 (0.55–0.97)		0.82 (0.67–1.00)		0.93 (0.78–1.11)	
P value	0.46791**		0.89580**		0.99830**		0.0162**		0.03697**		0.21211**	
ORR	23%	36%	19%	34%	16%	36%	42%	38%	36%	35%	35.%	36%

*, superiority; †, non-inferiority; **, not significant. CPS, combined positive score; ITT, intention-to treat; P, pembrolizumab; E, EXTREME regimen; PC, pembrolizumab plus chemotherapy; OS, overall survival; M, months; HR, hazard ratio; PFS, progression-free survival; NS, not significant; ORR, overall response rate.

Table 2 Summary of the post-hoc analysis of KEYNOTE-048 from EMA assessment report

Treatment arms	Pembrolizumab *vs.* EXTREME						Pembrolizumab plus chemotherapy *vs.* EXTREME					
PD-L1	CPS ≥20		1≤ CPS <20		CPS <1		CPS ≥20		1≤ CPS <20		CPS <1	
Treatment	P (N=133)	E (N=122)	P (N=124)	E (N=133)	P (N=44)	E (N=45)	PC (N=126)	E (N=110)	PC (N=116)	E (N=125)	PC (N=39)	E (N=43)
OS (median), M	14.8	10.7	10.8	10.1	7.9	11.3	14.7	11.0	12.7	9.9	11.3	10.7
HR (95% CI)	0.58 (0.44–0.78)		0.86 (0.66–1.12)		1.51 (0.96–2.37)		0.60 (0.45–0.82)		0.71 (0.54–0.94)		1.21 (0.76–1.94)	
P value	0.00010*		0.12827		0.96241		0.00044*		0.00726		0.78932	
PFS (median), M	3.4	5.3	2.2	4.9	2.1	6.2	5.8	5.2	4.9	4.9	4.7	6.2
HR (95% CI)	0.99 (0.76–1.29)		1.25 (0.96–1.61)		4.31 (2.63–7.08)		0.73 (0.55–0.97)		0.93 (0.71–1.21)		1.46 (0.93–2.30)	
P value	0.46791		0.95093		1.00000		0.0162**		0.29189		0.94898	
ORR	23%	36%	14%	33%	4.5%	42%	42%	38%	29%	33%	30%	39%

*, superiority; **, not significant. CPS, combined positive score; ITT, intention-to treat; P, pembrolizumab; E, EXTREME regimen; PC, pembrolizumab plus chemotherapy; OS, overall survival; M, months; HR, hazard ratio; PFS, progression-free survival; NS, not significant; ORR, overall response rate.

previous standard treatment with the EXTREME regimen in patients with previously untreated platinum-sensitive R/M SCCHN. However, the effectiveness of pembrolizumab alone and PF/CF plus pembrolizumab vary according to PD-L1 status (CPS). Hence, this new evidence should only be applied after close consideration of clinical situation and patient preference.

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Footnote

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